

## CLAIMS

1. A process for the preparation of estra-1,3,5(10)-trien-3,15 $\alpha$ ,16 $\alpha$ ,17 $\beta$ -tetraol (1) which comprises the steps of:
  - 5 1) converting estrone (7) into 3-A-oxy-estra-1,3,5(10),15-tetraen-17-one (6), wherein A is a protecting group;
  - 2) reduction of the 17-keto group of 3-A-oxy-estra-1,3,5(10),15-tetraen-17-one (6) to 3-A-oxy-estra-1,3,5(10),15-tetraen-17 $\beta$ -ol (5);
  - 3) protection of the 17-OH group of 3-A-oxy-estra-1,3,5(10),15-tetraen-17 $\beta$ -ol (5) to 3-A-oxy-17-C-oxy-estra-1,3,5(10),15-tetraene (4), wherein C is a protecting group;
  - 4) oxidizing the carbon-carbon double bond of ring D of 3-A-oxy-17-C-oxy-estra-1,3,5(10),15-tetraene (4) to protected estetrol (3); and
  - 5) removing the protecting groups, wherein preferably protecting group A is removed first to form 17-OC protected estetrol (2) and subsequently protecting group C is removed to form estetrol (1);wherein the protecting group A is selected from an C<sub>1</sub>-C<sub>5</sub> alkyl group or a C<sub>7</sub> - C<sub>12</sub> benzylic group and the protecting group C is selected from monofunctional aliphatic hydroxyl protecting groups.
- 20 2. Process according to Claim 1, wherein the protecting group is a C<sub>7</sub> - C<sub>12</sub> benzylic group.
3. Process according to Claim 2, wherein the protecting group is a benzyl group.
4. Process according to any one of Claims 1 - 3, wherein the protecting group C is selected from monofunctional aliphatic hydroxyl protecting groups.
- 25 5. Process according to Claim 4, wherein the monofunctional aliphatic hydroxyl protecting group is acetyl.
6. Process according to any one of Claims 1 - 5, wherein the reduction of the carbonyl group is carried out using a reducing agent selected from the group of metal hydride compounds.
- 30 7. Process according to claim 6, wherein the metal hydride compound is selected from the group consisting of LiAlH<sub>4</sub>, NaBH<sub>4</sub>, NaBH(OAc)<sub>3</sub>, ZnBH<sub>4</sub>, and NaBH<sub>4</sub>/CeCl<sub>3</sub>.

8. Process according to claim 7, wherein the metal hydride compound is  $\text{NaBH}_4$  in combination with  $\text{CeCl}_3$  hydrate.
9. Process according to any one of Claims 1 - 8, wherein the oxidation of the carbon carbon double bond in ring D is carried out with an oxidizing agent comprising osmium tetroxide.
10. Process according to claim 9, wherein the oxidizing agent is osmium tetroxide immobilized on PVP ( $\text{OsO}_4$ -PVP).
11. Process according to any one of the precedings Claims 1 - 10, wherein the oxidation of the carbon-carbon double bond in ring D is carried out with a catalytic amount of  $\text{OsO}_4$ -PVP.
12. Process according to any one of Claims 9 - 11, wherein  $\text{OsO}_4$ -PVP is used in combination with a co-oxidant.
13. Process according to Claim 12, wherein the co-oxidant is selected from the group consisting of trimethylamine-N-oxide, N-methyl morpholine-N-oxide or hydrogen peroxide.
14. Process according to Claim 13, wherein the co-oxidant is trimethylamine-N-oxide.
15. Process according to any one of Claims 1 to 14, wherein the protective  $\text{C}_7 - \text{C}_{12}$  benzylic group is removed by catalytic hydrogenation conditions.
16. Process according to Claim 15, wherein the catalytic hydrogenation conditions comprise a hydrogenation reaction using Pd on activated carbon under a hydrogen atmosphere.
17. Process according to any one of Claims 1 - 16, wherein the protective  $\text{C}_1 - \text{C}_5$  alkyl group is removed by using  $\text{BBR}_3$ .
18. A process for the preparation of 3-A-oxy-estra-1,3,5(10),15-tetraen-17-one (6) comprising the following steps:
  - (a1) conversion of the 3-OH group of estron (7) into a 3-AO group to form 3-A-oxy-estra-1,3,5(10)-trien-17-one (8);
  - (b1) conversion of the 17-keto group of 3-A-oxy-estra-1,3,5(10)-trien-17-one (8) into a protected keto group to form 3-A-oxy-17-D-estra-1,3,5(10)-triene (9);
  - (c1) halogenation of  $\text{C}_{16}$  of 3-A-oxy-17-D-estra-1,3,5(10)-triene (9) to form 3-A-oxy-16-X-17-D-estra-1,3,5(10)-triene (10) wherein X is a halogen atom

selected from the group chloride, bromide and iodide and wherein X is preferably bromide;

(d1) dehalogenation of 3-A-oxy-16-X-17-D-estra-1,3,5(10)-triene (10) to 3-A-oxy-17-D-estra-1,3,5(10),15-tetraene (11); and

5 (e1) deprotection of the protected keto group of 3-A-oxy-17-D-estra-1,3,5(10),15-tetraene (11) to form 3-A-oxy-estra-1,3,5(10),15-tetraen-17-one (6);

wherein A is selected from an C<sub>1</sub>-C<sub>5</sub> alkyl group, preferably a methyl group, or a C<sub>7</sub> - C<sub>12</sub> benzylic group, preferably a benzyl group, and wherein D is ethylene dioxo.

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19. A process the preparation of 3-A-oxy-estra-1,3,5(10),15-tetraen-17-one (6) comprising the following steps:

(a2) conversion of the 17-keto group of estron (7) into a protected keto group to form 17-D-estra-1,3,5(10)-trien-3-ol (12);

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(b2) conversion of the 3-OH group of 17-D-estra-1,3,5(10)-trien-3-ol (12) into a 3-AO group to form 3-A-oxy-17-D-estra-1,3,5(10)-trien-17-one (9);

(c2) halogenation of C<sub>16</sub> of 3-A-oxy-17-D-estra-1,3,5(10)-triene (9) to form 3-A-oxy-16-X-17-D-estra-1,3,5(10)-triene (10) wherein X is a halogen atom selected from the group chloride, bromide and iodide and wherein X is preferably bromide;

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(d2) dehalogenation of 3-A-oxy-16-X-17-D-estra-1,3,5(10)-triene (10) to 3-A-oxy-17-D-estra-1,3,5(10),15-tetraene (11); and

(e2) deprotection of the protected keto group of 3-A-oxy-17-D-estra-1,3,5(10),15-tetraene (11) to form 3-A-oxy-estra-1,3,5(10),15-tetraen-17-one (6);

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wherein A is selected from an C<sub>1</sub>-C<sub>5</sub> alkyl group, preferably a methyl group, or a C<sub>7</sub> - C<sub>12</sub> benzylic group, preferably a benzyl group, and wherein D is ethylene dioxo.

20. Process according to either one of Claim 18 or 19, wherein the protected keto group D is formed by converting the 17-keto group with ethylene glycol.

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21. Process according to any one of Claims 18 to 20, wherein steps (e1) and (e2) are carried out in the presence of a component selected from p-toluenesulfonic acid, pyridinium p-toluenesulfonate, and pyridinium chloride, preferably p-

toluenesulfonic acid, more preferably p-toluenesulfonic acid monohydrate using aqueous acetone as solvent.

22. Use of the product obtainable by the process of any of Claims 1 - 17 for the manufacture of a pharmaceutical composition, preferably for use in a method selected from a method of hormone replacement therapy, a method of treating vaginal dryness, a method of contraception, a method of enhancing libido, a method of treating skin, a method of promoting wound healing, and a method of treating or preventing a disorder selected from the group consisting of autoimmune diseases, breast tumours and colorectal tumours.
23. A cosmetic method of treating skin, wherein the method comprises the topical administration of the product obtainable by the process of any of Claims 1 - 17.
24. A compound according to formula 5, wherein A is selected from a C<sub>1</sub>-C<sub>5</sub> alkyl group or a C<sub>7</sub> - C<sub>12</sub> benzylic group.
25. A compound according to formula 4, wherein A is selected from a C<sub>1</sub>-C<sub>5</sub> alkyl group or a C<sub>7</sub> - C<sub>12</sub> benzylic group and C is selected from monofunctional aliphatic hydroxyl protecting groups.
26. A compound according to formula 3, wherein A is selected from a C<sub>1</sub>-C<sub>5</sub> alkyl group or a C<sub>7</sub> - C<sub>12</sub> benzylic group and C is selected from monofunctional aliphatic hydroxyl protecting groups.
27. A compound according to formula 2, wherein C is selected from monofunctional aliphatic hydroxyl protecting groups.
28. A compound according to formula 8, wherein A is a C<sub>7</sub> - C<sub>12</sub> benzylic group.
29. A compound according to formula 9, wherein A is selected from a C<sub>1</sub>-C<sub>5</sub> alkyl group or a C<sub>7</sub> - C<sub>12</sub> benzylic group and D is ethylene dioxy.
30. A compound according to formula 10, wherein A is selected from a C<sub>1</sub>-C<sub>5</sub> alkyl group or a C<sub>7</sub> - C<sub>12</sub> benzylic group, D is ethylene dioxy and X is halogen.
31. A compound according to formula 11, wherein A is selected from a C<sub>1</sub>-C<sub>5</sub> alkyl group or a C<sub>7</sub> - C<sub>12</sub> benzylic group and D is ethylene dioxy.